

(12) UK Patent Application

(19) GB (11) 2 240 472 (13) A

(43) Date of A publication 07.08.1991

(21) Application No 9101774.9

(22) Date of filing 28.01.1991

(30) Priority data

(31) 90306

(32) 29.01.1990

(33) IE

(51) INT CL⁵
A61K 31/565

(52) UK CL (Edition K)
A5B BHA B24Y B240 B241 B247 B828 B829 B841
U1S S2415

(56) Documents cited
None

(58) Field of search
UK CL (Edition K) A5B BHA BJA BJB
INT CL⁵ A61K
Online databases: WPI, CLAIMS, CHABS

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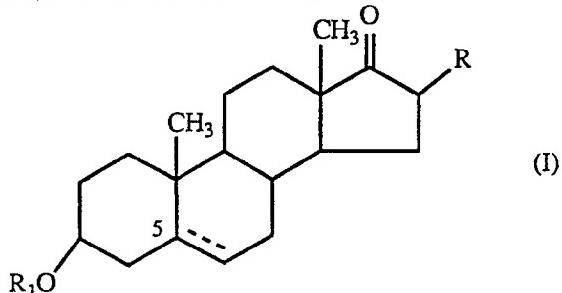
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(54) Agent for use in the prevention, control or reversal of hypertension

(57) Compounds of the formula (I)



in which R is a hydrogen or bromine atom and R₁ is a hydrogen atom, an SO₂OM group wherein M is a hydrogen or sodium atom, or a sulphatide, phosphatide or glucuronide group and wherein the broken line represents an optical double bond, and the hydrogen atom at position 5 is present in the α- or β-configuration or a mixture of both configurations are used for the manufacture of medicaments for use in the prevention, control or reversal of hypertension, especially essential hypertension.

GB 2 240 472 A

AGENT FOR USE IN THE PREVENTION CONTROL OR REVERSAL OF HYPERTENSION

This invention relates to the use of certain 17-ketosteroids in the prevention, control or reversal of hypertension, more particularly essential hypertension.

Essential hypertension, i.e. persistent high blood pressure with no known cause, afflicts a relatively high proportion of the general population. As essential hypertension is a chronic condition, generally with a requirement for long-term therapy with antihypertensive agents, it is desirable that such antihypertensive agents have minimal toxicity and side effects. The use of naturally occurring substances is favoured for use in such therapy.

Dehydroepiandrosterone (DHEA) and closely related analogues thereof have a wide range of activities in mammals.

Many of the 17-ketosteroids function as hormones and include sex hormones or precursors thereof and hormones which control metabolism. DHEA is one such 17-ketosteroid which is a precursor of both androgens and estrogens and additionally has important metabolic effects. These effects ensue from its inhibitory effect on enzymes such as glucose-6-phosphate dehydrogenase and NADH oxidase. Additionally, DHEA has an inhibitory effect on mitotic activity and on the permeability of membranes. The effect of DHEA on enzymes such as glucose-6-phosphate dehydrogenase and NADH oxidase leads above all to inhibition of the pentose cycle and of the cytochrome system, both of which restrict the supply of building materials and energy, necessary for biosynthetic processes, in particular for growth and regeneration of tissue. One of the main conditions of growth is an adequate supply of energy (ATP) and building materials for nucleic acid synthesis. DHEA controls both of these processes as an inhibitor of NADH oxidase and glucose-6-phosphate dehydrogenase. DHEA has been found to suppress some of the metabolic disorders and liver cirrhosis, and reduces pain in ischaemic heart disease, especially in angina pectoris, by restricting tissue respiration. DHEA has also been used in the treatment of menopause, emotional instability, depression and stress.

DHEA and related compounds are capable of reducing the colony forming ability of human peripheral blood mononuclear (PBM) cells infected with Epstein-Barr virus (a herpes virus) at concentrations of 10-100 µM (Carcinogenesis, Vol. 2, pp 883-886, 1981)

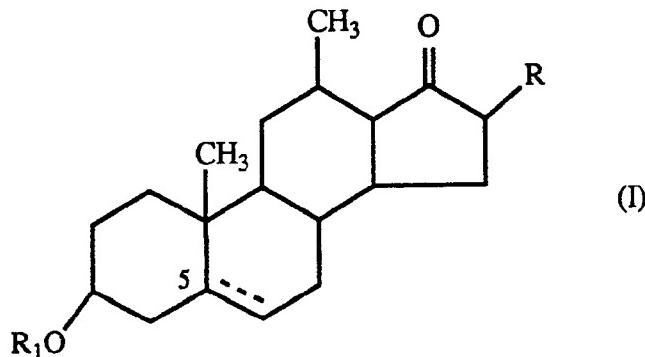
5 DHEA also inhibits complement activation and is therefore of value in the prophylaxis of hereditary angioneurotic oedema (Hidvegi et al., Complement 1; 201, 1984). DHEA also prevents autoantibody formation in the murine model of systemic lupus erythematosus (SLE).

10 GB 2 204 237 A describes and claims the use of DHEA and closely related analogues in the prophylaxis and therapy of retroviral infections, such as infection by HIV, or complications or consequences thereof. In particular, GB 2 204 237 A describes the use of DHEA and closely related analogues thereof in the prophylaxis and therapy of acquired immune deficiency syndrome (AIDS) and the related disease
15 AIDS related complex (ARC).

DHEA and closely related analogues thereof have not heretofore been proposed for use in the prevention, control or reversal of hypertension, more especially essential hypertension.

20 It is an object of the present invention to provide an agent for use in the prevention, control or reversal of hypertension, especially essential hypertension, which combines therapeutic efficacy with minimal side effects.

Accordingly, the invention provides use of a compound of the formula (I)



in which R is a hydrogen or bromine atom, and R₁ is a hydrogen atom, an SO₂OM group wherein M is a hydrogen or sodium atom, or a sulphatide, phosphatide or glucuronide group and wherein the broken line represents an optional double bond, and the hydrogen atom at position 5 is present in the α- or β-configuration or a mixture of both configurations, for the manufacture of a medicament for use in the prevention, control or reversal of hypertension, especially essential hypertension.

The effectiveness of the compounds of the formula (I) in the aforementioned treatment of hypertension can be demonstrated in recognised test procedures, for example by the reduction of Dexamethasone-induced hypertension in Sprague Dawley rats.

Preferred steroids covered by the general formula (I) are DHEA or hydrates, including polymorphs, enantiomers and isomers thereof or salts thereof, especially DHEA sulphate or the sodium salt thereof.

Pharmaceutical formulations for use in accordance with the invention contain at least one compound of the formula (I) and are administered systemically, by which is meant any mode or route of administration which results in effective levels of active ingredient appearing in the blood or at a site remote from the site of administration of said active ingredient.

Preferably the pharmaceutical formulation is formulated for oral or parenteral administration.

Suitable formulations for oral administration include hard or soft gelatin capsules, dragees, pills, tablets, including coated tablets, elixirs, suspensions, syrups or inhalations and controlled release forms thereof.

Because DHEA and like steroids and salts thereof are generally insoluble and exhibit poor bioavailability due to poor absorption when administered orally, the compounds of the formula (I) are suitably formulated as an enhanced bioavailability adsorbate formulation. Such adsorbate formulations comprise a mixture of one part by weight of a compound of the formula (I) and from 0.1 to 10 parts by weight of polyvinylpyrrolidone adsorbed on a cross-linked polyvinylpyrrolidone in a ratio of 1 part by weight of said mixture to 0.2 to 20 parts by weight of cross-linked polyvinylpyrrolidone.

Preferably the polyvinylpyrrolidone is present in the adsorbate in an amount of 0.1 to 2 parts by weight relative to 1 part by weight of the steroid.

Also preferably the formulation contains 1 part by weight of said mixture relative to 0.2 to 10 parts by weight of cross-linked polyvinylpyrrolidone.

A broad range of molecular weights of polyvinylpyrrolidones may be used (Mw 10,000 - 700,000) but a preferred polyvinylpyrrolidone is one where the average molecular weight is greater than 55,000, but is especially in the range 65,000 -250,000.

The polyvinylpyrrolidone is chosen to modify the solubility of the steroid in the presence of cross-linked polyvinylpyrrolidone and may also serve to maintain a level of amorphous drug in the polymer matrix structure of the adsorbate during dissolution. Principally, the polyvinylpyrrolidone serves to aid the enhanced bioavailability of the dosage form according to the invention.

An especially preferred cross-linked polyvinylpyrrolidone is Crospovidone (sold under the Trade Marks POLYPLASDONE XL (GAF) and KOLLIDON CL (BASF)).

For manufacturing formulations according to the invention the adsorbate may be blended with suitable excipients and used as a powder or as dispersible granules, or, it may be granulated and blended with a polymer or mixture of polymers or mineral material which cause the formulation to disintegrate in the presence of water, and tabletted or encapsulated according to conventional methods. These formulations exhibit improved drug absorption and enhanced bioavailability. Suitable polymers for blending with the adsorbates are inert polymers, which include water soluble polymers. Preferred polymeric and mineral materials which may be used include: natural starch (corn, potato, etc.) pregelatinised starch such as that sold under the Trade Mark AMIGEL, modified corn starch such as that sold under the Trade Mark STA R X 1500, sodium starch glycolate such as that sold under the Trade Marks PRIMOGEL and EXPLOTAB, sodium carboxymethylcellulose, carboxymethylcellulose, cellulose, methylcellulose, microcrystalline cellulose such as that sold under the Trade Mark AVICEL PH 101, ion exchange resins, cross-linked polyvinylpyrrolidone (Crospovidone) such as that sold under the Trade Marks POLYPLASDONE XL and KOLLIDON CL, clays such as aluminium magnesium silicate such as that sold under the Trade Mark VEEGUM HV, bentonite, colloidal silicon dioxide such as that sold under the Trade Mark AEROSIL, alginic acid or salts thereof, and gums such as agar, guar, locust bean, karaya, pectin and tragacanth gums. Bentonite is native colloidal hydrated aluminium silicate freed from gritty particles and consisting mainly of montmorillonite ($\text{Al}_2\text{O}_3 \cdot 4\text{SiO}_2 \cdot \text{H}_2\text{O}$). Bentonite swells in water to give a homogenous mass about 12 times the volume of the dry powder.

The adsorbates according to the present invention result in improved drug delivery relative to the micronised raw material, since the adsorbates in the formulations of the present invention yield an enhanced solubility complex leading to improved absorption and

bioavailability of said active drug *in vivo*, and enhanced *in vitro* dissolution rates in excess of 1.1 times that of the micronised free steroid having a particle size less than 10 µm (D50).

5 Solid dosage forms in addition to those formulated for oral administration include rectal suppositories.

The compounds of the formula (I) may also be administered in the form of an implant.

10 The compounds of the formula (I) may also be formulated for transdermal administration, for example, in the form of transdermal patches so as to achieve systemic administration.

Suitable injectable solutions include intravenous, subcutaneous and intramuscular injectable solutions.

The compounds of the formula (I) may also be administered in the form of an infusion solution or as a nasal inhalation or spray.

15 Pharmaceutical formulations for use in accordance with the invention are preferably administered in unit doses comprising from 1 to 1000 mg of active ingredient. Preferably, each unit dose comprises from 5 to 500 mg of active ingredient. However, the dosage will vary in accordance with the requirements of the individual patient as
20 determined by the attending physician. Pharmaceutical formulations for use in accordance with the invention can be administered as a single dosage or in several partial dosages in accordance with a treatment regimen as determined by the physician, according to the requirements of the individual patient. Indeed, in certain cases it may be sufficient to
25 administer an effective amount of a compound of the formula (I) as infrequently as once a week so as to achieve control of essential hypertension in accordance with the invention.

The present invention has particular application in subjects whose essential hypertension is associated with low or sub-normal levels of DHEA or conditions characterised by same.

The invention will be further illustrated by the following

5 Examples:

EXAMPLE 1

An adsorbate is prepared having the following composition:

DHEA	57.143% w/w
10 Polyvinylpyrrolidone	14.286% w/w
Crospovidone	28.571% w/w

The DHEA and polyvinylpyrrolidone are added to a suitable solvent such as acetone, dichloromethane or isopropanol and mixed until the solution is complete. Then the cross-linked polyvinylpyrrolidone (Crospovidone) is gradually added while mixing and the solvent evaporated. The resulting powder is reduced to obtain a finer particle size. X-ray diffraction and differential scanning calorimetry studies are performed on the powder and demonstrate that a proportion of the DHEA may be in an amorphous or altered crystalline state.

EXAMPLE 2

A powder formulation is prepared having the following composition:

DHEA adsorbate (prepared as in Example 1)	43.75% w/w
5 Sorbitol powder U.S.P.	23.00% w/w
ASPARTAME (ASPARTAME is a Trade Mark)	0.60% w/w
Lactose monohydrate U.S.P.	32.65% w/w

The above components are blended together and then a blend equivalent to 500 mg DHEA is packaged into suitable sachets.

10

EXAMPLE 3

A capsule formulation is prepared having the following composition:

DHEA adsorbate (prepared as in Example 1)	87.5% w/w
AEROSIL	2.5%
15 Lactose monohydrate U.S.P.	10.0% w/w

The above components are blended together and then a blend equivalent to 400 mg DHEA is filled into suitable capsules.

EXAMPLE 4

An adsorbate formulation is prepared having the following composition:

DHEA	40.00% w/w
5 Polyvinylpyrrolidone	20.00% w/w
Cross-linked polyvinylpyrrolidone	40.00% w/w

The DHEA and polyvinylpyrrolidone are added to a suitable solvent such as acetone, dichloromethane or isopropanol and mixed until the solution is complete. Then the cross-linked polyvinylpyrrolidone (POLYPLASDONE XL) is gradually added while mixing and the solvent evaporated.

EXAMPLE 5

A tablet formulation is prepared having the following composition:

DHEA adsorbate (prepared as in Example 4)	90.00% w/w
15 Cross-linked polyvinylpyrrolidone	9.50% w/w
Magnesium stearate	0.50% w/w

The above components are blended together and then compressed to form 300 mg DHEA tablets.

EXAMPLE 6

An adsorbate is prepared having the following composition:

DHEA sodium sulphate	57.15% w/w
Polyvinylpyrrolidone	14.28% w/w
5 POLYPLASDONE XL	28.57% w/w

The DHEA sodium sulphate and polyvinylpyrrolidone are added to a suitable solvent such as acetone, dichloromethane or isopropanol and mixed until the solution is complete. The POLYPLASDONE XL is added gradually while mixing and the solvent is evaporated.

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EXAMPLE 7

A capsule formulation is prepared having the following composition:

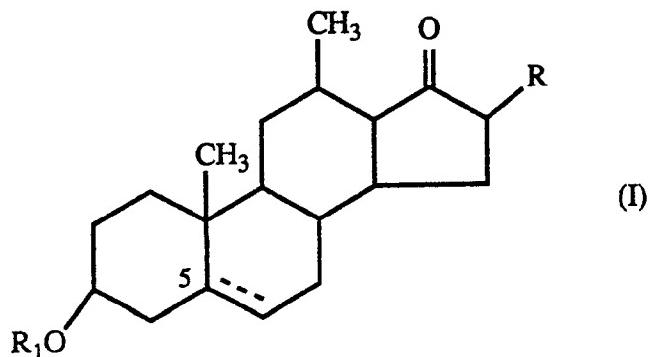
DHEA sulphate	87.50% w/w
AEROSIL	2.50% w/w
15 Lactose Monohydrate U.S.P.	10.00% w/w

The above components are blended together and then a blend equivalent to 500 mg DHEA base is filled into suitable capsules.

The invention is not limited to the embodiments described above which may be modified and/or varied without departing from the scope
20 of the invention.

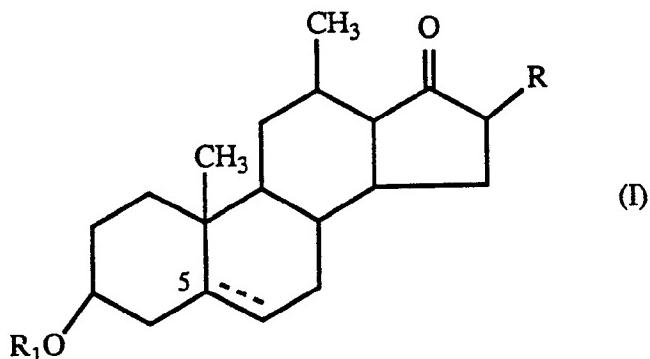
CLAIMS:

1. Use of a compound of the formula (I)



- 5 in which R is a hydrogen or bromine atom, and R₁ is a hydrogen atom, an SO₂OM group wherein M is a hydrogen or sodium atom, or a sulphatide, phosphatide or glucuronide group and wherein the broken line represents an optional double bond, and the hydrogen atom at position 5 is present in the α - or β -configuration or a mixture of both configurations, for the manufacture of a medicament for use in the prevention, control or reversal of hypertension.
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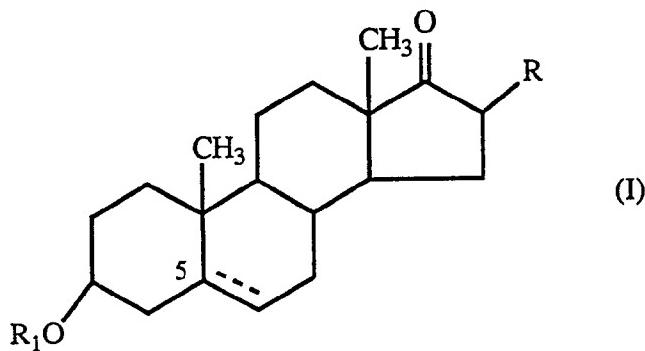
2. Use of a compound of the formula (I)



- in which R is a hydrogen or bromine atom, and R₁ is a hydrogen atom, an SO₂OM group wherein M is a hydrogen or sodium atom, or a sulphatide, phosphatide or glucuronide group and wherein the broken line represents an optional double bond, and the hydrogen atom at position 5 is present in the α- or β-configuration or a mixture of both configurations, for the manufacture of a medicament for use in the prevention, control or reversal of essential hypertension.
3. Use according to Claim 1 or 2, wherein the compound of the formula (I) is dehydroepiandrosterone (DHEA) or a hydrate, polymorph, enantiomer, isomer or salt thereof.
4. Use according to Claim 3, wherein the compound of the formula (I) is DHEA sulphate or the sodium salt thereof.
5. Use according to any one of Claims 1-4, wherein the compound of the formula (I) is formulated for oral or parenteral administration.
- 15 6. Use according to Claim 5, wherein the compound of the formula (I) is formulated for oral administration.
7. Use according to any preceding claim, wherein the compound of the formula (I) is administered to a subject whose hypertension is associated with low or sub-normal levels of DHEA or conditions characterised thereby.
- 20 8. Use according to Claim 1, substantially as hereinbefore described.

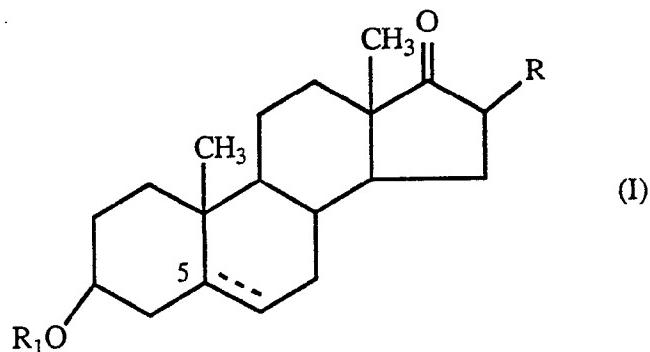
CLAIMS:

1. Use of a compound of the formula (I)



- 5 in which R is a hydrogen or bromine atom, and R_1 is a hydrogen atom, an SO_2OM group wherein M is a hydrogen or sodium atom, or a sulphatide, phosphatide or glucuronide group and wherein the broken line represents an optional double bond, and the hydrogen atom at position 5 is present in the α - or β -configuration or a mixture of both
10 configurations, for the manufacture of a medicament for use in the prevention, control or reversal of hypertension.

2. Use of a compound of the formula (I)



in which R is a hydrogen or bromine atom, and R₁ is a hydrogen atom, an SO₂OM group wherein M is a hydrogen or sodium atom, or a sulphatide, phosphatide or glucuronide group and wherein the broken line represents an optional double bond, and the hydrogen atom at position 5 is present in the α- or β-configuration or a mixture of both configurations, for the manufacture of a medicament for use in the prevention, control or reversal of essential hypertension.

- 5 3. Use according to Claim 1 or 2, wherein the compound of the formula (I) is dehydroepiandrosterone (DHEA) or a hydrate, polymorph, enantiomer, isomer or salt thereof.
- 10 4. Use according to Claim 3, wherein the compound of the formula (I) is DHEA sulphate or the sodium salt thereof.
5. Use according to any one of Claims 1-4, wherein the compound of the formula (I) is formulated for oral or parenteral administration.
- 15 6. Use according to Claim 5, wherein the compound of the formula (I) is formulated for oral administration.
7. Use according to any preceding claim, wherein the compound of the formula (I) is administered to a subject whose hypertension is associated with low or sub-normal levels of DHEA or conditions characterised thereby.
- 20 8. Use according to Claim 1, substantially as hereinbefore described.